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I. THE STEREOCHEMICAL COURSE OF THE HYDROGENOLYSIS OF ARYL OXIRANES AND BENZYL ALCOHOLS

II. HYDROBORATION-OXIDATION OF ENEAMINES

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THE STEREOCHEMICAL COURSE OF THE HYDROGENOLYSIS OF ARYL OXIRANES AND BENZYL ALCOHOLS

INTRODUCTION

There has been considerable study of Raney nickel and palladium-charcoal catalyzed hydrogenolysis of benzyl-oxygen bonds. These reactions proceed mainly to give debenzylation, e.g. the palladium-charcoal catalyzed hydrogenolysis of benzylphenyl ether gives toluene and phenol (1), and Raney nickel catalyzed hydrogenolysis of styrene oxide yields 2-phenylethanol (2).

In an effort to elucidate the mechanism of hydrogenolysis-debenzylation reactions, a number of stereochemical studies have been made. Karns (3) has discussed many of the earlier investigations, as well as his own, relating to the stereochemical course of hydrogenolysis of not only benzyl-oxygen bonds, but also of benzyl-sulfur and benzyl-halogen bonds.

In one of the earlier studies, Bonner (4) showed that the methyl and ethyl esters of optically active atrolactic acid, upon Raney nickel catalyzed hydrogenolysis, gave the esters of 2-phenylpropionic acid, predominantly with retention of configuration. He found the methyl ethers of the hydroxy esters to behave similarly.

In contrast to this, Mitsui and Imaizumi (5,6,7) found that the Raney nickel hydrogenolysis of the phenyl ether, the acetate, propionate, or benzoate of optically active ethyl atrolactate gave ethyl-2-phenylpropionate, predominantly with inversion of configuration. The authors explained these results, as well as other debenzylation-hydrogenolysis reactions, on the basis of the ability of the group attached to the benzyl oxygen to be adsorbed to the catalyst and to the steric influences about the benzyl carbon.

Moreover, Karns' studies of oxirane benzylic oxygens (3), using palladium-charcoal as catalyst, showed that hydrogenolysis of optically active α-methylstyrene oxide and 2 α, 3 α-oxido-3 β -phenylcholestane proceeded by debenzylation with a high level of inversion at the benzyl carbon to give optically active 2-phenylpropanol and 3 α-phenylcholestane-2 α-ol, respectively. Of the mechanisms proposed by Karns (3) for palladium-charcoal hydrogenolysis of aryl

oxiranes, he favored the one which depicted the adsorption of the oxide to the catalyst through the phenyl group. He suggested that initial transfer of a "hydrogen species" (that is, the equivalent of H^+,H^-, or $H\cdot$) from catalyst to the benzyl carbon by an Sn2 type process, with resultant ring opening, followed by addition of a corresponding hydrogen species to the oxygen, would account for the inverted product.

In contrast to the stereochemical behavior on palladium-charcoal, Karns (3) observed that the Raney nickel catalyzed hydrogenolysis of optically active α-methylstyrene oxide showed little stereospecificity and yielded 2-phenylpropanol with predominant racemization, but with a small preference for inversion of configuration. In addition, he showed that the Raney nickel catalyzed hydrogenolysis of 2α, 3 α-oxido-3 α-phenylcholestane gave the thermodynamically more stable possible isomer, 3 β-phenylcholestane and 3β-phenylcholestane-2 β-ol, by apparent retention of configuration.

The recent observation of Garbish (8) suggests that the above Raney nickel hydrogenolysis might be the result of an equilibration of the product initially formed. Garbish has reported, contrary to an earlier publication (9), that

the Raney nickel hydrogenolysis of either of the 3-phenylcholestane-3-ols proceeds by retention of configuration, and that 3α-phenylcholestane equilibrates on Raney nickel to the thermodynamically more stable β isomer.

Karns has also shown that the hydrogenolysis of the hydroxyl group of optically active ethyl atrolactate on palladium-charcoal gave ethyl-2-phenylpropionate with predominant inversion of configuration. Of the possible mechanisms for this reduction, Karns favored the one which depicted the hydrogenolysis proceeding by adsorption on the catalyst of the phenyl group and the oxygen atom of the carbonyl group, followed by an Sn2 type attack of a hydrogen species from the catalyst at the benzyl carbon to produce the inverted ester.

It appeared reasonable from these studies that further examination of the stereochemical course of catalytic hydrogenolysis of aryl oxiranes and benzyl alcohols would be both interesting and desirable.

DISCUSSION

In the present work threo and erythro-2,3-diphenyl-2-butanol were selected for further stereochemical studies of palladium-charcoal hydrogenolysis of the benzyl hydroxyl group. In addition, the stereospecificity of catalytic hydrogenolysis of aryl oxiranes was examined in two cyclic examples, 1-phenylcyclohexene oxide and 1-phenylcyclopentene oxide. At the outset of this work neither one of these oxides had been prepared in pure form.

Earlier attempts (10) to obtain 1-phenylcyclohexene oxide from the reaction of 1-phenylcyclohexene and perbenzoic acid resulted in the isolation of 2-phenylcyclohexanone, as the major product as a result of a partial rearrangement of the oxide during distillation. However, when the undistilled product from this reaction was treated with ammonia (10), trans-2-amino-1-phenylcyclohexanol was obtained in 40% yield, showing the crude oil to contain at least 40% oxide. In addition, when 1-phenylcyclohexene was treated with

monoperphthalic acid, phenylcyclohexane trans-1,2-diol, formed from the intermediate oxide, was isolated in 80% yield (11).

In the present work, an attempt was made to eliminate isomerization and dec mposition in the peracid approach by treating 1-phenylcyclohexene with perbenzoic acid at 0^{o}. Absorption at 5.94 μ in the infrared spectrum of the crude product indicated that partial isomerization of the oxide to the ketone had occurred even under these conditions.

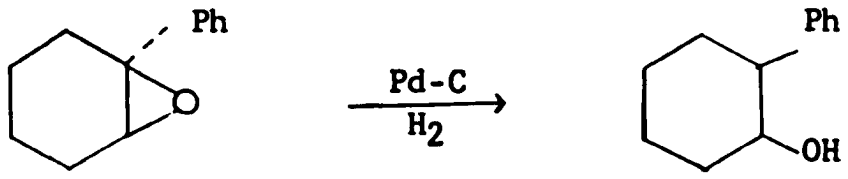
To avoid exposure of the oxide to acid, a synthesis by way of the bromohydrin, followed by ring closure with alkali, was developed. The olefin, 1-phenylcyclohexene, was converted to the corresponding bromohydrin by treatment with an aqueous suspension of N-bromosuccinimide. Distillation of the product led to extensive decomposition, so the crude bromohydrin was treated directly with aqueous sodium hydroxide solution. Consumption of 48% of the base theoretically required occurred at room temperature and no further reaction was noted after 0.5 hours. Low temperature flash and fractional distillations gave the pure oxide in 36% yield.

In addition to a satisfactory elementary analysis, the infrared spectrum of the oxide did not have carbonyl, hydroxyl, or olefinic absorption bands and showed

characteristic oxide bands (12), 8.05, 11.06 and 12.2 μ.

Hydrogenolysis of 1-phenylcyclohexene oxide was carried out in ethyl acetate with a trace of pyridine on 15% palladium-charcoal catalyst under 36 p.s.i. of hydrogen. Pyridine was employed to prevent an isomerization similar to that reported by Karns (3), who found that α-methylstyrene oxide isomerized spontaneously to hydrotropaldehyde upon contact with Pd-C catalyst, presumably due to catalysis by traces of acid.

After hydrogenation (8 hours) cis-2-phenylcyclohexanol in 91% yield was obtained by fractional crystallization of the reaction product. The solid was identified by its melting point, which was not depressed when admixed with an authentic sample, as well as by its infrared spectrum, which was identical with that of cis-2-phenylcyclohexanol. The infrared spectrum of the oily crystalline residue from fractional crystallization was identical to the spectrum of a commercial mixture of cis and trans-2-phenylcyclohexanol. Thus, the hydrogenation proceeded mainly by debenzylation and inversion at the benzyl carbon of the oxide as shown below:



To verify that the stereospecificity displayed was not due to selective reduction of the ketone which might be produced by an isomerization of the oxide, 2-phenylcyclohexanone was submitted to the hydrogenation conditions used for the epoxide. The ketone was recovered unchanged.

The assignment of the cis and trans configurations to the isomeric 2-phenylcyclohexanols, m.p. 42° and 58°, respectively, rests upon an abundance of chemical evidence. The expected trans alcohol was produced by a Walden inversion type reaction upon treatment of cyclohexene oxide with phenyllithium (13). This was the same isomer obtained by hydroboration of 1-phenylcyclohexene, followed by peroxide oxidation (14). Brown (15) has given overwhelming evidence that this sequence proceeds through a cis anti-Markownikoff addition to the double bond to give the trans alcohol.

The same alcohol was the main product obtained upon equilibration of a mixture of the cis- and trans-2-phenylcyclohexanols with aluminum isopropoxide, isopropyl alcohol,

and a small amount of acetone. Previous studies (16) have shown an equilibration of this type yields mainly the more stable, lower energy isomer, which, by employing a conformational argument analogous to that used by Eliel and coworkers (16), should be the trans isomer.

Further chemical evidence for the assignment of the stereostructures of the alcohols came from the products obtained on pyrolysis of the methyl xanthates and acetates of these alcohols, reactions known to proceed by cis elimination (17). The methyl xanthate and acetate of the lower melting isomer gave mainly 3-phenylcyclohexene, the olefin expected from the cis derivatives, while the corresponding derivatives of the higher melting trans alcohol yielded 1-phenylcyclohexene.

Contrary to the results obtained with palladium-charcoal, Raney nickel catalyzed hydrogenolysis of the oxide, under identical conditions, was not stereospecific. The infrared spectrum of the oil obtained disclosed the presence of a mixture of cis and trans-2-phenylcyclohexanol, and the absence of 1-phenylcyclohexanol. By employing the gas chromatographic retention times of the pure cis and pure trans alcohols, the oil was shown to contain 5 parts trans alcohol and 3.8 parts cis alcohol, as well as 2.1 parts of

an unidentified material that emerged from the column much faster than the alcohols. This compound probably was phenylcyclohexane, but this was not confirmed. As previously mentioned, a complete reduction of this type had been observed by Karns (3) in the Raney nickel catalyzed hydrogenation of 2α, 3α-oxido-3β-phenylcholestane, which yielded in considerable amount, 3β-phenylcholestane.

Again these results may not show the true stereochemistry of the Raney nickel hydrogenolysis of 1-phenylcyclohexene oxide, since the compounds might be obtained after equilibration of initially formed products (8).

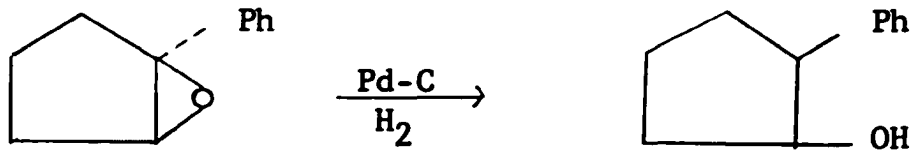
To investigate further the palladium-charcoal catalyzed, stereospecific, hydrogenolysis of aryl oxiranes, efforts were made to prepare 1-phenylcyclopentene oxide, which had not been reported in a pure form. The procedure described earlier for obtaining pure 1-phenycyclohexene oxide yielded dark brown, viscous oils which failed to afford pure oxide. Moreover, our own and earlier observations (18) showed that treatment of 1-phenylcyclopentene with perbenzoic or monoperphthalic acid at 0^{o} produced mainly 2-phenylcyclopentanone by an acid-catalyzed isomerization of the oxide. Although this isomerization took place even upon buffering perbenzoic acid with inorganic bases as strong as

sodium carbonate, apparently no isomerization occurred on treatment of 1-phenylcyclopentene with monoperphthalic acid at -17° to -20°. The latter reaction, after completion as shown by iodometric titration, yielded a colorless oil whose elementary analysis showed a content of oxygen somewhat too high for the pure oxide. However, the infrared spectrum showed the absence of carbonyl, hydroxyl and olefinic compounds, and had present characteristic oxide peaks at 10.85, 11.45 and 11.9 μ (12). This crude oxide was hydrogenated without further purification since distillation of a test sample caused considerable decomposition and isomerization to carbonyl compounds.

Palladium-charcoal catalyzed hydrogenolysis of 1-phenylcyclopentene oxide was carried out under the same conditions used for 1-phenylcyclohexene oxide. A pale brown oil was obtained which displayed carbonyl and hydroxyl absorptions in the infrared spectrum. Substitution of a trace of 10% sodium hydroxide solution for the pyridine in the hydrogenation did not prevent the formation of the carbonyl compounds, and it seemed advantageous to revert to the original procedure. An effort to separate the carbonyl and hydroxyl compounds by fractional distillation was unsuccessful, but refluxing the hydrogenated oxide with Girard's

reagent T and then washing with water removed the bulk of the carbonyl compounds. The residual oil still displayed a weak ester carbonyl absorption in the infrared spectrum, and therefore, it was refluxed in aqueous sodium hydroxide. A small amount of crude solid acid was obtained. Since the original crude oxide did not show a carbonyl or hydroxyl peak in the infrared spectrum, and its elementary analysis did have too high a content of oxygen, the trace amount of ester apparently was derived from a peroxy ether during hydrogenation.

The remaining neutral oil was distilled to give 2-phenylcyclopentanol in 63% yield, and proved to be mainly the cis alcohol with only a trace of the trans isomer. Thus the hydrogenolysis of the oxide went mainly as shown below, by debenzylation and inversion at the benzyl carbon of the oxide with the same stereospecificity observed for the Pd-C reduction of phenylcyclohexene oxide:



Unlike the former case where both cis and trans-2-phenylcyclohexanol were available, and well characterized, at the outset of this work only trans-2-phenylcyclopentanol had been previously reported by Tallent (19) who obtained it from reaction of phenyllithium with cyclopentene oxide. Therefore, it was convenient to carry out the identification of the hydrogenated oxide by comparing it with the trans-2-phenylcyclopentanol and the isomeric mixture of cis and trans alcohols. The possibility that the alcohol from hydrogenolysis was 1-phenylcyclopentanol was discounted, not only since debenzylation was expected, but also because the reduced oxide gave a good yield of the tosylate derivative.

For comparison, trans-2-phenylcyclopentanol was produced by hydroboration of 1-phenylcyclopentane followed by basic hydrogen peroxide oxidation of the alkylborane and corresponded in every respect to that reported by Tallent (19). The infrared spectrum of the trans alcohol and the one from hydrogenation were very similar, but these alcohols were not the same since a mixture of the phenylurethane derivatives melted low and over a broad range.

In addition, the mixture of cis and trans-2-phenylcyclopentanol, made by lithium aluminum hydride reduction of 2-phenylcyclopentanone, had an infrared spectrum comparable

with that of the alcohols from hydrogenolysis and the trans alcohol. By peak area evaluation of the gas chromatographic retention times of the alcohols from the lithium aluminium hydride reduction and that of the alcohol mixture from hydrogenolysis of the oxide, the latter was shown to be 91.9% cis and 8.9% trans-2-phenylcyclopentanol.

The possibility that the stereospecificity observed was due to hydrogenation of 2-phenylcyclopentanone, which might be produced by isomerization of the oxide, was discounted, since the ketone was not reduced under the conditions used for the epoxide.

The stereospecificity observed with Pd-C catalyzed hydrogenolysis of these oxides can be explained by the mechanism favored by Karns (3). The adsorption of the aryl oxirane to the catalyst is established through the aryl group, followed by an Sn2 type attack by a hydrogen species from the catalyst at the benzyl carbon to cause an inversion at this point with debenzylation. The cis alcohols are produced after the addition of a hydrogen species to the oxygen atom of the partially reduced intermediate.

If adsorption of the aryl oxiranes to the catalyst is attained through the phenyl group, then replacing this group with an alkyl group, which would have practically no

tendency to be adsorbed, should produce a slower, or no, hydrogenation. To check this postulate, 1-methylcyclohexene oxide was chosen. Previous publications have reported the hydrogenolysis of this oxide using two different procedures. One involved acetic acid and palladium-charcoal (20), while the other employed ethyl acetate with a trace of perchloric acid as solvent and Adams platinum oxide (21). By means of the melting point diagram of the 3,5-dinitrobenzoates of cis and trans-2-methylcyclohexanols, the former reduction was estimated to yield 50% cis and 50% trans alcohol, and the latter hydrogenolysis was shown to produce 58% of trans and 42% cis alcohol (21). Infrared spectroscopy of the mixed products from the reduction using Adams catalyst showed neither 1-methylcyclohexanol nor 1-methylcyclopentylmethanol (21). The reduction mechanism was depicted by McQuillen and Ord (21) as protonolysis of the oxide, followed by ring opening to provide a more easily reducible cationic intermediate, which was then reduced by hydrogen transfer from the catalyst to either side of the cation.

The products obtained from the reductions described above and from the Pd-C catalyzed hydrogenolysis of aryl oxiranes indicated two different modes of hydrogenation. Since the aryl oxide reductions were carried out in the

presence of a trace amount of base, attempts were made to reduce 1-methylcyclohexene oxide under similar conditions.

A sample of 1-methylcyclohexene oxide was made by the usual procedure from 1-methylcyclohexene and monoperpthalic acid (11). This oxide, unlike the aryl oxiranes, was prepared and was distilled without isomerization or decomposition. Attempted hydrogenations of the oxide gave no uptake of hydrogen under the following conditions: (1) Pd-C, 15% in ethyl acetate and a trace of pyridine with 40 p.s.i. of hydrogen for 12 hours; (2) Pd-C, 15% in absolute ethanol with a potassium hydroxide pellet and 37 p.s.i. of hydrogen for 12 hours; (3) Pt-C, 5% in absolute ethanol and 42 p.s.i. of hydrogen for 12 hours; and (4) PtO_2, in absolute ethanol and 36 p.s.i. of hydrogen for 12 hours.

After the solvents were removed, the residual oils were distilled at atmospheric pressure to give essentially unchanged 1-methylcyclohexene oxide as shown by infrared spectroscopy.

The resistance to reduction displayed by 1-methylcyclohexene oxide as compared with the aryl oxiranes could be due to the more stable oxide ring possessed by the alkyl oxiranes. This greater stability was demonstrated by the resistance of the oxide to isomerization under preparative

conditions and by its ability to be distilled readily without rearrangement or decomposition.

In addition, 1-methylcyclohexene oxide might not be adsorbed to the catalyst as readily as the aryl oxiranes, since an alkyl and not a phenyl group is at the α position, and hydrogen transfer from catalyst to oxide should be less favorable.

For further study, erythro and threo-2,3-diphenyl-2-butanol were selected for examination of the stereochemical course of Pd-C hydrogenolysis of benzyl alcohols. The configurations of these alcohols were established earlier by applying stereospecific synthetic methods (22), including use of the asymmetric induction rule as it applies to ketones, and the hydroboration-oxidation of the α,α'-dimethylstilbene isomers. In addition, the configurations of the expected hydrocarbons, meso and d,l-2,3-diphenylbutane, are known (22), making it possible to study the stereochemical course of the hydrogenations.

Pure erythro-2,3-diphenyl-2-butanol was obtained by a Wittig rearrangement of bis-(α-methylbenzyl)ether, followed by distillation and fractional crystallization of the reaction products (23). The residual oil from the fractional crystallizations, upon column chromatography yielded first

unreacted ether, followed by more of the erythro alcohol and finally impure threo-2,3-diphenyl-2-butanol (24). Recrystallization of the threo alcohol from hexane lowered its melting point, indicating a concentration of the erythro isomer.

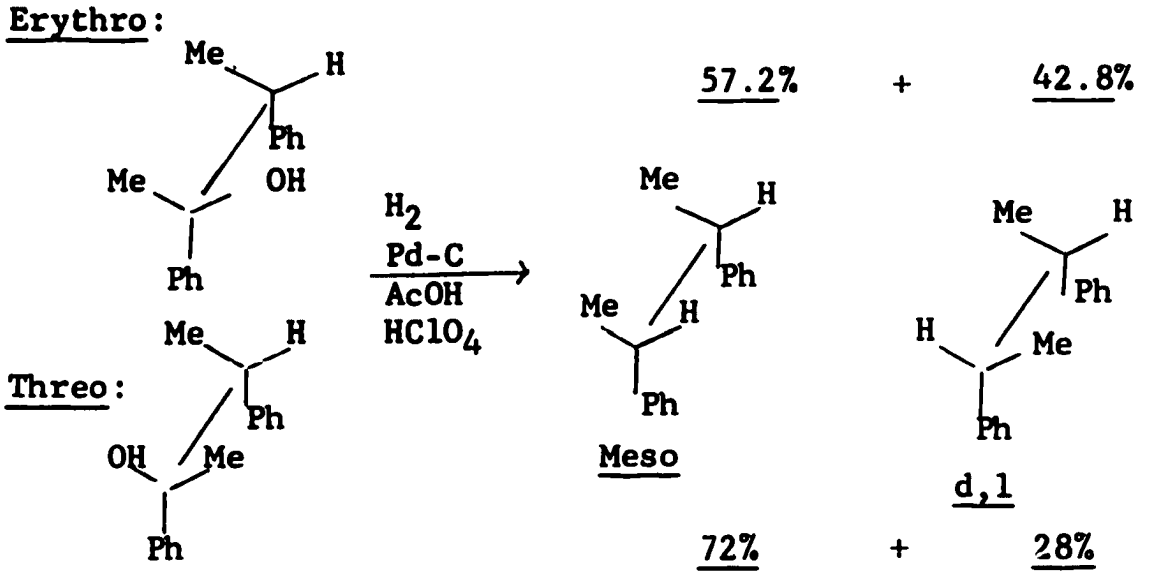
The pure threo alcohol was made conveniently by the stereospecific Pd-C catalyzed hydrogenolysis of cis-α,α'-dimethylstilbene oxide (22). The threo alcohol produced in this manner was recrystallized from hexane and obtained in a pure form.

The cis- α,α'-dimethylstilbene oxide was obtained from the reaction of monoperphthalic acid and cis- α,α'-dimethylstilbene, which was prepared according to the procedure of Hauser and co-workers (25) by the trans dehydrohalogenation of threo-2-chloro-2,3-diphenylbutane. The chloro compound was produced by a lithium amide dimerization of α-methylbenzyl chloride (25).

The Pd-C catalyzed hydrogenations of pure erythro and threo-2,3-diphenyl-2-butanol were carried out in a solution of acetic acid with a trace of perchloric acid, under 40 p.s.i. of hydrogen for 2 hours, after which hydrogenation was complete. Previous experiments showed the presence of perchloric acid to be necessary for the hydrogenation. The more severe conditions needed for the hydrogenation of these

alcohols as compared with that of the aryl oxides might be expected, since the strained, 3-membered oxirane ring is more reactive than a hydroxyl group. The infrared spectrum of the hydrogenated material indicated complete reduction of the alcohols by the absence of the characteristic alcohol absorption bands and the presence of the peaks for 2,3-diphenylbutane at 9.25, 9.50 and 9.75 μ (22).

On the basis of previous work (3) and our own observations with the aryl oxiranes, we anticipated the Pd-C catalyzed hydrogenolysis of these alcohols to proceed through a similar inversion at the benzyl carbon with replacement of the hydroxyl group. The hydrogenolysis of threo-2,3-diphenyl-2-butanol yielded 72% of the expected meso-2,3-diphenylbutane and 28% of the d,l isomer, as shown by vapor phase chromatographic analysis. However, hydrogenolysis of the erythro alcohol gave only 42.8% of the inverted d,l isomer and 57.2% of the thermodynamically more stable meso hydrocarbon. These reductions may be summarized as follows:



Further investigation of this hydrogenation showed that when the erythro alcohol was submitted to hydrogenation conditions for 50 hours, 28% d,l and 72% meso hydrocarbon was obtained, indicating isomerization of 17.2% of the original d,l hydrocarbon to the more stable meso form. In contrast, the meso compound, when subjected to hydrogenation conditions for 93 hours, was recovered unchanged. However, the slow isomerization of d,l to meso hydrocarbon does not affect the ratio of products from the hydrogenolysis of the alcohols, since no conversion of the d,l isomer occurred under hydrogenation conditions for 2 hours (the time necessary for hydrogenation of the alcohols). Moreover, when hydrogenation of the erythro alcohol was stopped after one-half hour and the partially hydrogenated material

chromatographed to separate the alcohol and hydrocarbons, the hydrocarbon mixture showed the same ratio of d,l to meso isomer as in the completed hydrogenolysis.

The results obtained from the reduction of the erythro alcohol are not compatible with those reported by Karns (3). However, unlike optically active ethyl atrolactate, dehydroxylation by hydrogenolysis of erythro and threo-2,3-diphenyl-2-butanol can lead to diastereoisomers that have different thermodynamic stabilities. Since both erythro and threo alcohols gave mainly the more stable diastereoisomer (the meso hydrocarbon), the differences in stabilities of the possible products apparently affected the outcome of the hydrogenolysis. The threo alcohol gave a higher percentage of the meso hydrocarbon, apparently with inversion, than did the erythro isomer, which gave the meso compound by retention of configuration.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

1-Phenylcyclohexene. 1-Phenylcyclohexene was prepared according to the method of Eliel, McCay and Price (26). 1-Phenylcyclohexanol, m.p. 61-62°, which was made by cyclohexanone and phenylmagnesium bromide, was dehydrated by heating with an equal weight of potassium acid sulfate at 140-150° for 1.5 hours. Fractional distillation gave the pure olefin (66%), b.p. 106-108° (5.5 mm.), n_D^{25} 1.5670; reported: n_D^{25} 1.5666, b.p. 128° at 16 mm. (26).

2-Bromo-1-Phenylcyclohexanol. To a suspension of 18 g. (0.113 mole) of N-bromosuccinimide in 100 ml. of water maintained at 25°, 15.8 g. (0.1 mole) of 1-phenylcyclohexene was added with vigorous stirring over a period of 15 to 20 minutes. After 12 hours of stirring at room temperature, the mixture was extracted with three 50 ml. portions of ether. The combined ether washings were dried over anhydrous sodium sulfate, and the ether was removed at room temperature in

vacuo (10 mm.). The crude bromohydrin, 28.28 g. (98%), showed strong hydroxyl absorption in the infrared and gave a positive halogen test.

Attempts to prepare the corresponding chlorohydrin following the Organic Synthesis procedure for cyclohexene chlorohydrin, as reported by Hiskey (27), yielded both a white solid (m.p. 99-100°) and a yellow oil. Since the solid gave a negative halogen test and did not have hydroxyl absorption in the infrared spectrum, it was not investigated further. The yellow oil gave a positive halogen test but displayed only a weak hydroxyl absorption in the infrared spectrum. Distillation of this oil caused considerable decomposition.

1-Phenylcyclohexene Oxide. The crude 2-bromo-1-phenylcyclohexanol (50.5 g., 0.198 mole), was stirred vigorously at room temperature with 250 ml. of 1.16 N sodium hydroxide. By titration of aliquot portions of the base with standard hydrochloric acid at intervals, it was shown that the reaction was complete in less than 0.5 hours, and that only 48% of the required base had reacted. After 0.75 hours, the water phase was separated and extracted three times with 50 ml. portions of ether. The combined organic phase was washed with water until the washings were neutral

to pH paper, dried over anhydrous sodium sulfate, and the ether removed at room temperature in vacuo (7 mm.). The crude residue gave a positive halogen test, and the infrared spectrum showed very little hydroxyl absorption. The oil was first flash distilled at 35-70° (0.05 to 0.001 mm.) and then fractionally distilled. The colorless oxide (1-phenyl-7-oxabicyclo- 4,1,0 - heptane), b.p. 48-53° at 0.007 mm., n_D^{27} 1.5377, d_4^{27} 1.0768, obtained in 36% yield (12 g.), showed neither carbonyl nor hydroxyl absorption in the infrared spectrum, and gave a negative halogen test.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10; O, 9.18

Found : C, 82.81; H, 7.84; O, 9.59.

Trans-2-Phenylcyclohexanol. Trans-2-phenylcyclohexanol, m.p. 57-58°, reported m.p. 57-58° (26), was prepared by equilibration of the commercially available mixture of cis and trans isomers of 2-phenylcyclohexanol with aluminum isopropoxide, according to the procedure of Eliel, McCay, and Price (26).

2-Phenylcyclohexanone. Crude 2-phenylcyclohexanone was obtained by oxidation of the commercial mixture of the 2-phenylcyclohexanols (310 g.) with chromium trioxide in acetic acid, according to the method of Price and Karabinos (28). The ketone was purified by conversion to the semicarbazone,

which was recrystallized from ethanol-water until a melting point of 190-191° was obtained. The semicarbazone (16.9 g.), on steam distillation with an equal weight of phthalic anhydride gave 10 g. of pure 2-phenylcyclohexanone, m.p. 61-62°; reported m.p. 61-62° (28). The infrared spectrum of this material showed a strong carbonyl band at 5.9 μ.

Cis-2-Phenylcyclohexanol. 2-Phenylcyclohexanone (3 g.) was hydrogenated with Raney nickel in ethanol, according to the procedures of Cornubert, et al. (29). After two recrystallizations from hexane, 1.2 g. of pure cis-2-phenylcyclohexanol, m.p. 41-42°, was obtained; reported m.p. 41-42° (29).

Hydrogenolysis of 1-Phenylcyclohexene Oxide with 15% Palladium-Charcoal. A solution of 7.83 g. of oxide, 25 ml. of ethyl acetate, and 3 drops of pyridine was shaken with 1 g. of 15% palladium-charcoal under 36 p.s.i. of hydrogen for 10 hours. Hydrogen uptake ceased at the end of 8 hours. The mixture was filtered, and the solvent removed. Three crops, totaling 7.2 g. (91.3% yield), of cis-2-phenylcyclohexanol (m.p. 41-42°) were obtained by fractional crystallization from hexane. No melting point depression was observed when this alcohol was mixed with authentic cis alcohol (29). The infrared spectrum of the oily crystalline residue from the

fractional crystallization was identical with that of the commercial mixture of cis and trans-2-phenylcyclohexanol.

Hydrogenolysis of 1-Phenylcyclohexene Oxide with Raney Nickel. A mixture of 2 g. of oxide, 25 ml. of ethyl acetate, and 2 g. of Raney nickel wet with ethanol was shaken under 36 p.s.i. of hydrogen for 18 hours. After 10 hours the hydrogen uptake ceased. The oil obtained after filtration and removal of solvent was gas chromatographed on a column (100' x 0.01") packed with di-n-decyl phthalate. By comparison of the retention times of authentic samples of cis and trans-2-phenylcyclohexanol (26,29), and estimation by peak areas, the oil was shown to consist of 5.0 parts trans alcohol, 3.8 parts cis alcohol, and 2.1 parts of a fraction that emerged from the column before the alcohols. The ratio of cis and trans alcohol indicates that upon Raney nickel hydrogenolysis of the oxide 56.9% retention and 43.1% inversion of configuration took place. The infrared spectrum of the oil from hydrogenolysis was essentially the same as that of a commercial mixture of 2-phenylcyclohexanol.

Stability of 2-Phenylcyclohexanone to Hydrogenation. 2-Phenylcyclohexanone (5 g., m.p. 61-62°) in 25 ml. of ethyl acetate and 2 drops of pyridine was shaken under 36 p.s.i. of hydrogen for 24 hours in the presence of 2 g. of 15% palladium-

charcoal. After filtration and removal of solvent, 4.7 g. of 2-phenylcyclohexanone (m.p. 59-61°) was recovered. Its infrared spectrum was the same as that of the starting material and showed no hydroxyl absorption.

1-Phenylcyclopentene. Crude 1-phenylcyclopentanol, produced by the reaction of phenylmagnesium bromide with cyclopentanone, was dehydrated with formic acid according to the procedure of Baddely, Chadwick, and Taylor (30) to give crude 1-phenylcyclopentene. Fractional distillation gave the colorless olefin in 63% yield, b.p. 112-113° (8 mm.), n_D^{25} 1.5740; reported n_D^{25} 1.5734 (31), b.p. 107-108° (12 mm.) (30).

1-Phenylcyclopentene Oxide. To a solution of 33 g. (0.228 mole) of 1-phenylcyclopentene in 75 ml. of ether, held at dry ice temperature, 0.238 mole of monoperphthalic acid in 570 ml. of ether was added slowly with stirring. After the addition was complete, the reaction flask was stored at -17 to -20° for 10 days, when the reaction was complete as shown by iodometric titration. To the cool organic solution, 500 ml. of cool 1 N sodium hydroxide was added with stirring, and the organic phase was separated and washed with water until the washings were neutral to pH paper. After the ether solution was dried over anhydrous sodium

sulfate, the ether was removed at room temperature in vacuo. The infrared spectrum of the colorless oil, n_D^{25} 1.5418, obtained in 95.5% yield (35 g.) showed neither the presence of carbonyl compounds nor absorption bands associated with the olefin. Since decomposition occurred upon attempted distillation, the oxide was used without further purification.

Anal. Calcd. for $C_{11}H_{13}O$: C, 81.92; H, 8.13; O, 9.95

Found : C, 81.26; H, 6.97; O, 11.90

Hydrogenolysis of 1-Phenylcyclopentene Oxide. After the addition of 1.5 g. of 15% palladium-charcoal to a solution of 13 g. of the oxide in 35 ml. of ethyl acetate and 3 drops of pyridine, the mixture was shaken under an atmosphere of 36 p.s.i. of hydrogen. Although the hydrogen uptake ceased after 7 hours, the hydrogenation was continued 5 hours longer. The mixture was filtered and the solvent removed. The infrared spectrum of the residual, light brown oil (n_D^{25} 1.5448), had strong carbonyl and hydroxyl absorption bands. The crude oil was refluxed for 1 hour in a solution of 9 g. of Girard's T reagent in 100 ml. of ethanol, 50 ml. of water, and 4.5 g. of glacial acetic acid. The reaction mixture was then poured into 400 ml. of 5 N sodium hydroxide solution, and the precipitated oil was extracted with 3 portions of ether. The ether extracts were washed with water, dried over sodium

sulfate, and the ether removed. Since the oil obtained still showed a very weak carbonyl absorption in its infrared spectrum, it was refluxed for 2 hours with sodium hydroxide in an ethanol-water solution. Excess water was added, and the oil that separated was extracted with ether. The aqueous solution was acidified, and a very small amount of solid acid precipitated. The ether extracts were washed with water, dried over sodium sulfate, and the ether removed. The alcohol was distilled at 114-119° (3.3 mm.) to give 9 g. of colorless oil (n_D^{25} 1.5452), with 0.7 g. of dark residue left in the distillation flask. The infrared spectrum of the purified alcohol showed strong hydroxyl absorption but no carbonyl band. Gas chromatographic analysis on a column (100' x 0.01") packed with di-n-decyl phthalate, showed on evaluation of peak areas the mixture was composed of 91.1% cis and 8.9% trans-2-phenylcyclopentanol.

Anal. Calcd. for $C_{11}H_{13}O$: C, 81.44; H, 8.70; 0, 9.87

Found : C, 80.99; H, 8.80; 0, 10.20

Cis-2-Phenylcyclopentyl-p-Toluenesulfonate. To a cool solution (0°) of the above distilled alcohol mixture (2 g.) and pyridine (25 ml.), 3 g. of p-toluenesulfonyl chloride was added. The reaction mixture was kept at 0° for 17 hours and then poured into dilute sulfuric acid. A single

recrystallization of the crude ester (1.8 g.) from absolute ethanol gave 1 g. of colorless crystals, m.p. 96-97°, which was unchanged by further recrystallizations. This derivative had decomposed after standing about 2.5 weeks.

Anal. Calcd. for $C_{18}H_{20}O_3S$:

C, 68.33; H, 6.37; S, 10.01

Found : C, 68.44; H, 6.42; S, 10.01

Phenylurethane of Cis-2-Phenylcyclopentanol. In a flask equipped with condenser and drying tube, 2 g. of phenyl isocyanate was added to a solution of 2 g. of the above alcohol mixture dissolved in 20 ml. of hexane. After refluxing 0.75 hours, the reaction was cooled (0°) and 3 g. of white crystals were collected by filtration. One recrystallization from carbon tetrachloride and two from hexane yielded 2.2 g. of the phenylurethane, m.p. 99.5-100.5°.

Anal. Calcd. for $C_{18}H_{19}O_2N$:

C, 76.83; H, 6.81; N, 4.99

Found : C, 76.85; H, 6.82; N, 5.32

Trans-2-Phenylcyclopentanol. In a nitrogen atmosphere, excess boron trifluoride etherate (10 ml., 0.079 mole) was added over a period of 1 hour to a stirred mixture of 5 g. (0.0346 mole) of 1-phenylcyclopentene and 1.3 g. (0.034 mole) of lithium aluminum hydride in 100 ml. of dry ether.

After the mixture was stirred an additional 3 hours, a saturated water solution of sodium sulfate was added, and the mixture was filtered. The organic phase was separated, dried over anhydrous sodium sulfate and the ether was removed. The oil residue was dissolved in 100 ml. of 80% ethanol (v/v) containing 4 g. (0.1 mole) of sodium hydroxide, and 15 g. 30% hydrogen peroxide (0.132 mole of H_2O_2) and refluxed for 2 hours. Water was added to the solution, and the precipitated oil was extracted with three portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, and the ether removed. The residue was distilled at 123-127° (4 mm.) to give 3.0 g. (54% yield) of trans-2-phenylcyclopentanol, n_D^{25} 1.5472; reported n_D^{25} 1.5478 (19).

Phenylurethane of Trans-2-Phenylcyclopentanol. The phenylurethane was prepared by the same procedure used for that of cis-2-phenylcyclopentanol. After two recrystallizations from hexane, the melting point obtained was 81-82°; reported, 82-83° (19). Mixed with the phenylurethane of cis-2-phenylcyclopentanol, it melted over a range of 69-75°.

Anal. Calcd. for $C_{18}H_{19}O_2N$:

C, 76.83; H, 6.81; N, 4.99

Found : C, 77.04; H, 7.04; N, 4.99

2-Phenylcyclopentanone. 2-Phenylcyclopentanone was

made by the procedure of Mislow and Hamermesh (32). 2-Chlorocyclopentanone (b.p. 85-88° at 11 mm.; n_D^{25} 1.4740) prepared from chlorine and cyclopentanone, was added to an equivalent amount of phenylmagnesium bromide. The ether was removed by distillation and replaced by toluene. The reaction was refluxed for 5 hours then poured into ice and dilute hydrochloric acid solution. The organic phase was extracted by ether, washed with 5% sodium hydroxide solution, and dried over sodium sulfate. After removal of ether the crude ketone was fractionally distilled, and the fraction distilling at 142-145° (10 mm.) was recrystallized from hexane to give pure 2-phenylcyclopentanone, m.p. 35-36°, 45% based on 2-chlorocyclopentanone; reported m.p. 35-36° (32).

Cis and Trans-2-Phenylcyclopentanol. A solution of 2 g. of 2-phenylcyclopentanone in 100 ml. of anhydrous ether was added over a period of 25 minutes to a stirred mixture of 1.5 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. After 3 hours of additional stirring with refluxing, 250 ml. of 20% sodium hydroxide solution was added to the cooled mixture (0°). The reaction mixture was filtered to remove insoluble hydroxides and the aqueous phase of the filtrate was extracted twice with ether. The ether extracts were combined with the organic phase, dried over anhydrous

sodium sulfate, and the ether was removed. The infrared spectrum of the residual oil indicated that complete reduction had occurred. This mixture of 2-phenylcyclopentanols, containing about 35% cis and 65% trans as shown by peak area evaluation of the v.p.c. curve, was used for comparison and confirmation of retention times of the alcohols from hydrogenolysis of the oxide.

Attempt to Hydrogenate 2-Phenylcyclopentanone. A solution of 5 g. of 2-phenylcyclopentanone (32), m.p. 35-36°, 25 ml. of ethyl acetate, and a trace of pyridine was shaken with 0.5 g. of 15% palladium-charcoal under 36 p.s.i. of hydrogen for 24 hours. After filtration and the removal of solvent, 4.7 g. of 2-phenylcyclopentanone (m.p. 34-35°) was recovered. The infrared spectrum of the material obtained was identical with that of the starting material and showed no hydroxyl absorption.

1-Methylcyclohexene Oxide. This oxide was prepared by a procedure similar to that of Norgrei, Horivity, and Filler (11). Crude 1-methylcyclohexanol, produced from the reaction of methylmagnesium iodide and cyclohexanone, was dehydrated by refluxing at 120-130° in the presence of an equal weight of zing chloride for 2.5 hours. The 1-methylcyclohexene was distilled at 106° (1 atm.), n_D^{25} 1.4470 (60%

yield), and then mixed with an ether solution containing an equivalent amount of monoperphthalic acid. The mixture was stored at 0^{o} to 5^{o} for three days, at which time the reaction was shown to be complete by iodometric titration. The ether solution was washed first with sodium carbonate solution and then with water until the washings were neutral to pH paper. After the ether solution was dried over sodium sulfate and the ether removed, the residual oil was distilled at 135^{o} (740 mm.) to give pure oxide, n_D^{25} 1.4407 (63% based on the amount of olefin used); reported n_D^{25} 1.4410, b.p. 135^{o} at 1 atm. (11).

Bis-(α-Methylbenzyl)Ether. The ether was made according to the procedure of Weinheimer (23). α-Methylbenzyl alcohol (250 g.) was added to 100 ml. of a 1:1 (volume) solution of sulfuric acid and water, keeping the temperature below 35^{o}. After the addition, the reaction mixture was stirred for an additional six hours at room temperature and the organic phase extracted with three portions of ethyl ether. The combined organic phases were washed with water, sodium bicarbonate solution, again with water and dried over sodium sulfate. After removal of the solvent, the oil was distilled to give the colorless ether in 85% yield, b.p. 141^{o} (4 mm.), n_D^{22} 1.5409; reported n_D^{25} 1.5391 (23).

Erythro and Threo-2,3-Diphenyl-2-Butanol. The Wittig rearrangement of bis-(α-methylbenzyl)ether to give erythro and threo-2,3-diphenyl-2-butanol was carried out according to the procedure of Sifford (24). Bis-(α-methylbenzyl)ether (150 g., 0.664 mole), dissolved in an equal volume of ethyl ether, was added to a stirred suspension of potassium amide prepared from 1 atom of potassium and 1.5 l. of liquid ammonia. When the addition was complete, the ammonia and ethyl ether were allowed to evaporate from the flask and the reaction mixture heated to 50°. After 5 days at this temperature, with constant stirring, the product was hydrolyzed with an excess of water and extracted with three portions of ether. The organic phase was washed with water until the washings were neutral to pH paper, dried over sodium sulfate, and the solvent removed. The residual oil was distilled and the fraction collected at 135-147° (4 mm.) was mixed with an equal volume of hexane and cooled to 0°. The solid obtained after filtration was recrystallized twice from hexane, to give 10 g. of pure erythro-2,3-diphenyl-2-butanol, m.p. 84-86°; reported m.p. 84-86° (24). After removal of the hexane from the fractional crystallizations, 49.6 g. of oil was obtained. In the same manner as used by Sifford (24), 35.65 g. of this residual oil was

chromatographed through a basic alumina column (5.5 x 100 cm.). The forerun gave 19.67 g. of unreacted bis-(α-methylbenzyl)ether. The second fraction was crude erythro alcohol, which was recrystallized from an acetic acid-water solution to give 5.29 g. of pure erythro isomer. A third cut yielded 9 g. of crude threo-2,3-diphenyl-2-butanol, m.p. 60-63°, which was contaminated with enough erythro isomer that recrystallization from hexane gave a mixture of alcohols, which according to the melting point (55-59°), contained more erythro isomer than the original crude material.

Threo-2-Chloro-2,3-Diphenylbutane. This compound was prepared according to the procedure of Hauser and coworkers (25). To a stirred suspension of lithium amide prepared from 0.916 atom of lithium and 1.5 l. of liquid ammonia, a solution of α-methylbenzyl chloride (129 g., 0.9175 mole) in an equal volume of ether, was added over a twenty minute period. Lithium amide was used since it was not strong enough to cause dehydrohalogenation of the dimeric product. After stirring for 4.75 hours, at which time the liquid ammonia had evaporated, the mixture was filtered and the filtrate washed with a 2 N hydrochloric acid solution, followed by 10% sodium carbonate solution and then dried over sodium sulfate. The ether was removed at room temperature

in vacuo and the oil residue was diluted with an equal volume of hexane. Cooling to 0° gave upon filtration 20 g. of threo-2-chloro-2,3-diphenylbutane, m.p. 63-65°. Two recrystallizations from hexane raised the melting point to 67-68°; reported 67-68° (25). The hexane used for crystallization of the threo isomer was removed at room temperature in vacuo to give 100 g. of the crude liquid, erythro-2-chloro-2,3-diphenylbutane.

Cis and Trans-α,α'-Dimethylstilbene. The procedure followed for this preparation was that of Hauser et al. (25). An ether solution of threo-2-chloro-2,3-diphenylbutane (19.3 g., 0.0819 mole) was added during 2 to 3 minutes to a stirred suspension of sodium amide made from 0.0819 atom of sodium and 250 ml. of liquid ammonia. After 3 hours of additional stirring, water was added and the ether layer separated. The organic phase was washed with water, dried over sodium sulfate and the ether was removed. After the residual oil was taken up in methanol and cooled to 0°, 11 g. of cis- α, α'-dimethylstilbene was obtained on filtration, m.p. 65-66°; reported 65-66° (25). Using a procedure similar to the above, crude erythro-2-chloro-2,3-diphenylbutane (80 g.) gave trans- α, α'-dimethylstilbene. The dehydrohalogenation was carried out with a 50% excess of potassium

amide suspended in liquid ammonia. After the product was purified by four recrystallizations from methanol, 12 g. of trans- α, α'-dimethylstilbene was obtained, m.p. 104-106°; reported 105-106° (25).

Cis and Trans-α,α'-Dimethylstilbene Oxide. To a cool ether solution of 5 g. (0.024 mole) of cis-α,α'-dimethylstilbene, 0.0244 mole of monoperphthalic acid, dissolved in 45 ml. of ether, was added so the temperature did not rise above 10°. After ten days at 0°, the reaction mixture was washed with 10% sodium hydroxide and then with water until the washings were neutral. The organic solution was then dried over sodium sulfate and the ether removed, yielding 5.05 g. of oxide, m.p. 49-51°. One recrystallization from methanol raised the melting point to 52-53°; reported 51-52° (22).

In the same manner as above, a quantitative yield of trans-α,α'-dimethylstilbene oxide (m.p. 108-110°) was obtained from trans-α,α'-dimethylstilbene; reported m.p. 108.5-110° (22).

Threo-2,3-Diphenyl-2-Butanol. To 5 g. of cis-α,α'-dimethylstilbene oxide in 25 ml. of 95% ethanol, 2 g of 10% Pd-C was added and the mixture shaken for 6.5 hours under 35 p.s.i. of hydrogen. The mixture was filtered and the solvent

removed. The residual oil crystallized on long standing (m.p. 61-64°) and after three recrystallizations from hexane, 3.4 g. of pure threo alcohol was obtained, m.p. 65-67°; reported 65-67° (24).

Hydrogenolysis of Pure Erythro and Threo-2,3-Diphenyl-2-Butanols. Hydrogenolysis of both alcohols was carried out in the same manner. The alcohol (1 g.) was hydrogenated in 25 ml. of acetic acid containing 2 drops of 70% perchloric acid with 0.25 g. of 5% palladium-charcoal under 40 p.s.i. of hydrogen for 2 hours. After filtration, the solution was added to 55 ml. of hexane and washed repeatedly with water, until the washings were neutral to pH paper. The organic phase was dried over sodium sulfate and the hexane was removed. The infrared spectra in both cases showed the absence of hydroxyl absorption and displayed characteristic 2,3-diphenylbutane peaks as 9.25, 9.50, and 9.75 μ (21). Analysis was carried out by gas chromatography through a column (8' x ¼") packed with 20% Apiezon L on Chromsorb A/W. The analysis by peak area evaluation showed reduction of the erythro alcohol to give 42.8% d,l and 57.2% meso hydrocarbon, and the reduction of the threo alcohol to give 28% d,l and 72 meso hydrocarbon.

At the outset, in an attempt to find conditions for

hydrogenolysis, the erythro alcohol was not hydrogenated in acetic acid or in a mixture of acetic acid and acetic anhydride. When ethyl acetate with a trace of 70% perchloric acid was employed as solvent for hydrogenation of the erythro alcohol, a solid was obtained whose infrared spectrum showed neither alcohol nor hydrocarbon bands, but displayed characteristic acetate peaks at 5.78 and 8.1μ. Identification of this impure and oily white solid was not undertaken.

SUMMARY

Pure 1-phenylcyclohexene oxide was made for the first time by an aqueous sodium hydroxide ring closure of the crude bromohydrin, 2-bromo-1-phenylcyclohexanol, followed by flash and fractional distillation at very low pressure. As shown by comparison with authentic samples, the palladium-charcoal catalyzed hydrogenolysis of this oxide gave 91% cis-2-phenylcyclohexanol, while hydrogenolysis on Raney nickel gave 5.0 parts trans alcohol, 3.8 parts cis alcohol, and 2.1 parts of unidentified material, or 56.7% retention and 43.1% inversion according to the cis and trans alcoholic mixture.

Although pure 1-phenylcyclopentene oxide was not obtained, this oxide was produced in a form uncontaminated with olefinic, carbonyl or hydroxyl compounds. The Pd-C hydrogenolysis of this impure oxide gave the expected alcohols, as well as some carbonyl compounds. After separation and distillation, the alcoholic mixture was shown to be

91.1% cis and 8.9% trans-2-phenylcyclopentanol by comparison with the pure trans compound and the cis and trans isomeric mixture.

Thus, palladium-charcoal hydrogenolysis of both aryl oxiranes proceeded by debenzylation, mainly with inversion at the benzyl carbon of the oxirane. The stereospecificity displayed with Pd-C could not be due to the corresponding ketones which might be produced by isomerization of the oxide during hydrogenolysis, since neither ketone reduced under the hydrogenation conditions used for the oxides. 1-Methylcyclohexene oxide also was not hydrogenated under the same or similar conditions as used for the aryl oxiranes.

The threo and erythro-2,3-diphenyl-2-butanols were synthesized and hydrogenated on Pd-C. The threo alcohol gave 72% of the more thermodynamically stable isomer, meso-2,3-diphenylbutane, apparently by inversion, and 28% of the d,l hydrocarbon by retention of configuration. The erythro alcohol yielded by inversion only 42.8% of the d,l hydrocarbon and 57.2% of the more stable meso isomer by retention. A conversion of the d,l isomer to the meso hydrocarbon was observed under hydrogenation conditions. However, this isomerization was too slow to affect the ratio of hydrocarbons in the hydrogenolysis of the alcohols.

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HYDROBORATION-OXIDATION OF ENEAMINES

INTRODUCTION

In the recent book, "Hydroboration," Brown (1) discusses numerous additions of diborane to unsaturated linkages (hydroboration), and the reactions of the organoboranes obtained. The hydroboration of an olefin gives a quantitative yield of the corresponding alkylborane. Important aspects of the course of the olefinic hydroboration are that the addition of diborane to the olefin proceeds: 1. through an apparent four-center transition state; 2. in a cis fashion; 3. so that the boron is found almost entirely on the less hindered olefinic carbon (2).

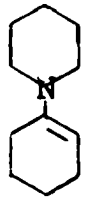
Oxidation with alkaline hydrogen peroxide converts the alkylboranes to the corresponding alcohols with retention of configuration (2). Therefore, the over all hydroboration-oxidation reaction gives anti-Markowinkoff, cis hydration of the olefin.

In contrast to the olefins, the hydroboration-

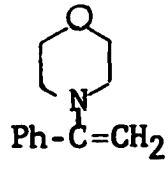
oxidation of certain vinyl sulfides and vinyl ethers gave many different products (3). To determine the synthetic value of hydroboration-oxidation in other heterosubstituted vinyl systems, the investigation of certain eneamines was undertaken. The eneamines studied were of two types, one derived from ketones and the other from aldehydes.

DISCUSSION

The first group of eneamines was obtained from the corresponding ketones by refluxing the desired carbonyl compound and secondary amine in benzene or toluene and removing the water produced by means of a Dean-Stark separator (4). In this manner 1-(1-cyclohexenyl)piperidine (I) was obtained from cyclohexanone and piperdine, 4-(α-styryl)morpholine (II) from acetophenone and morpholine, and 4-(1-phenyl-1-propenyl)morpholine (III) from propiophenone and morpholine.



(I)



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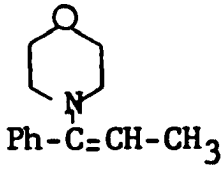


(III)

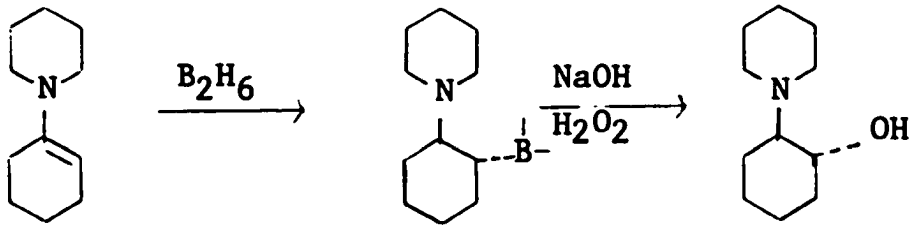
These eneamines have both an amino group and a phenyl or alkyl substituent located on the same vinyl carbon, while the other vinyl carbon contains at least one hydrogen. Therefore, if the hydroboration-oxidation proceeded as in the olefinic cases, the steric influences of these groups on the eneamine would favor the production of the corresponding

vicinal aminoalcohol.

The above eneamines were hydroborated in situ with a 3 to 5 molar excess of diborane generated from sodium borohydride and an excess of boron trifluoride etherate in dry tetrahydrofuran. The organoboranes obtained were treated with excess alkaline hydrogen peroxide and the reaction products separated into neutral and basic fractions by extraction with dilute hydrochloric acid.

Using this procedure, the known trans-2-(1-piperidino)cyclohexanol was obtained in an 88% yield from 1-(cyclohexenyl)piperidine. In this case, hydroboration proceeded predominantly as in the olefins, by a cis addition of diborane to the carbon-carbon double bond with boron adding to the least hindered carbon (equation 1). The trans aminoalcohol was obtained on alkaline peroxide oxidation of the organoborane (equation 1).

Equation 1



The infrared spectrum of the trace amount of neutral fraction was similar to that of cyclohexanol. However, the

3,5-dinitrobenzoate of this material was a mixture that could not be purified.

The hydroboration and oxidation of 4-(1-phenyl-1-propenyl)morpholine gave the expected vicinal aminoalcohol, 1-(4-morpholino)1-phenyl-2-propanol in 88% yield. Identification of this material was based on its infrared spectrum (hydroxyl at 2.92 μ; morpholinic ether at 8.95 μ), upon its elemental analysis and that of its hydrochloride salt, and upon analogy of its synthesis with the preceding example.

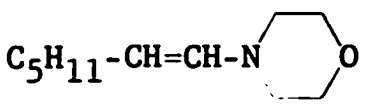
The small amount of unidentified neutral material obtained displayed both hydroxyl and carbonyl absorptions in the infrared spectrum.

The reaction of the least hindered eneamine, 4-(α-styryl)morpnoline, produced the vicinal aminoalcohol, 2-(4-morpholino)-2-phenylethanol, in 71% yield. As before, identification was based on the infrared spectrum (hydroxyl at 2.95 μ, morpholinic ether at 8.95 μ), and upon its elemental analysis and that of the picrate derivative. The infrared spectrum of the small amount of neutral fraction showed carbonyl and hydroxyl absorptions.

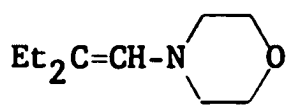
Thus, the hydroboration-oxidation of these aryl and alkyl eneamines proceeded to give mainly the corresponding vicinal aminoalcohol expected on the basis of the steric

influences.

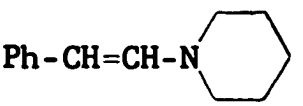
The second group of eneamines, derived from the aldehydes, was synthesized by the method of Mannich (5,6,7). This consisted of forming the geminal diamine (aminal), from 1 mole of aldehyde and 2 moles of secondary amine in the presence of a drying reagent which removed the water formed during the reaction. Pyrolysis of the aminal under reduced pressure eliminated one mole of amine to give the desired eneamine on distillation. By this procedure, which is particularly useful for carbonyl compounds that have a tendency to condense with themselves in the presence of secondary amines, 4-(1-heptenyl)morpholine (IV) was obtained from heptanal and morpholine; 4-(2-ethyl-1-butenyl)morpholine (V) from 2-ethylbutyraldehyde and morpholine; and 1-(β-styryl) piperidine (VI) from phenylacetaldehyde and piperidine.



(IV)



(V)



(VI)

Since there is less steric hindrance about the amino substituted vinyl carbon in this group of eneamines, hydroboration would be expected to give more boron addition at this position than was observed with the first group. More specifically, the steric influences alone in 4-(1-heptenyl)-

morpholine would not appear to favor addition of boron to either vinyl carbon. Addition to the alkyl substituted vinyl carbon would give the corresponding vicinal amino-alcohol, while addition to the amino substituted vinyl carbon would be expected to yield the aldehyde (heptanal) from decomposition of the initially formed geminal aminoalcohol.

The hydroboration-oxidation of 4-(1-heptenyl)morpholine gave the expected vicinal aminoalcohol, 1-(4-morpholino)-2-heptanol (45% yield) as indicated by the infrared spectrum (hydroxyl at 2.95μ and morpholinic ether at 8.95μ), by its elemental analysis and that of its picrate derivative, and upon analogy of its formation with that of trans-2-(1-piperidino)cyclohexanol.

Instead of the aldehyde, the neutral fraction of this reaction gave the alcohol, 1-heptanol (43%), as proved by its infrared spectrum and by the melting point of its α-napthylurethane derivative. Vapor phase chromatographic data revealed the absence of 2-heptanol. Since an ex situ hydroboration gave the same results as the in situ, the excess boron trifluoride present in the latter was not necessary for the formation of this neutral alcohol.

In the hydroboration of 4-(2-ethyl-1-butenyl)morpholine, less boron would be expected to add to the dialkyl

substituted, vinyl carbon due to the steric factor involved. Thus, less vicinal aminoalcohol should be obtained than in the previous case. Actually, the hydroboration of this compound yielded a very small amount of basic material which apparently was a mixture, since the picrate derivative melted over a broad range. Its infrared spectrum had a hydroxyl absorption at 2.90μ and a morpholinic ether band at 8.97μ.

The neutral fraction, which accounted for 82% of the starting material, was shown to be 2-ethylbutanol by infrared spectroscopy and by the melting point of its 3,5-dinitrobenzoate.

In order to determine the overall requirement of diborane needed for hydroboration, a stoichiometric study was made. The crude products obtained were identified by infrared spectroscopy. It was assumed that all the hydrogen of sodium borohydride was available as B_2H_6, according to equation 2 (8).

Equation 2

$$3NaBH_4 + 4BF_3 \xrightarrow{THF} 3NaBF_4\downarrow + 4BH_3{:}THF$$

An in situ hydroboration-oxidation, conducted with a molar ratio of borane to 4-(2-ethyl-1-butenyl)morpholine of

1.17 to 1, resulted mainly in the recovery of the starting material. A small amount of neutral 2-ethylbutanol was obtained contaminated with a trace of carbonyl component, presumably 2-ethylbutanal. The aldehyde probably was formed by hydrolysis of the eneamine during its exposure to dilute hydrochloric acid in the separation of the neutral and basic fractions.

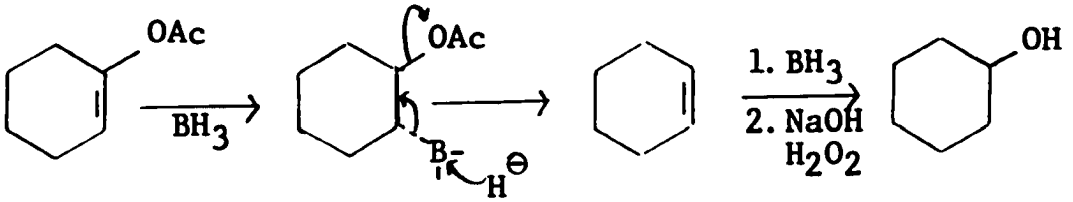
Complete hydroboration was observed with a molar ratio of 1.38 to 1 of borane to eneamine. The main product was shown to be 2-ethylbutanol and the basic fraction was identical with that obtained in the preparative reaction; apparently no eneamine was present.

The failure of hydroboration in the equimolar reaction indicates the formation of an eneamine-borane complex. This is supported by the fact that amine-borane complexes do not hydroborate carbon-carbon double bonds except at elevated temperatures (100-200^{o}) (9).

Several mechanisms could be proposed to explain the production of the neutral alcohol. In an analogous hydroboration-oxidation reaction, Hassner *et al.* (10) obtained both *trans*-1,2-cyclohexandiol and an unexpected product, cyclohexanol, from 1-acetoxycyclohexene. Two possible paths were considered for the formation of the mono alcohol. The

first consisted of hydroboration of the enol acetate to give the 1-acetoxyalkylborane, which proceeded to the alcohol by some unknown mechanism. The second path was depicted as the hydroboration of the enol acetate to give the 2-acetoxyalkylborane, the common intermediate for both normal and abnormal products (equation 3). This precursor, on elimination of the elements of $-\dot{B}-O-\overset{O}{\overset{\|}{C}}-CH_3$, could yield cyclohexene that would then be hydroborated and oxidized in the usual manner to give cyclohexanol. Neither of the above mechanisms was preferred by the authors.

Equation 3



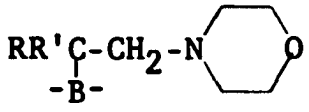
Prior to Hassner's work, olefins had been isolated from the hydroboration-oxidation of several enol carboxylates (11). However, their formation apparently took place during oxidative treatment and not during hydroboration, since excess diborane was used and would have added to any alkene present.

In the hydroboration-oxidation of eneamines, the

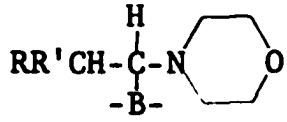
neutral alcohols evidently were not formed from the olefins obtained by an elimination of the 2-aminoalkylborane (VII). This conclusion is partially based on the fact that the reaction of 4-(1-heptenyl)morpholine gave 1-heptanol free of any 2-heptanol. Hydroboration-oxidation of terminal straight chain olefins is known to give, in addition to the primary alcohol, the secondary alcohol in 4 to 6% yield (12). Moreover, hydroboration of 4-(1-heptenyl)morpholine for periods of 3 or 20 hours gave the same yield of neutral alcohol. If the alcohol were obtained from the olefin, longer periods of hydroboration would be expected to give more oelfin and thus a larger yield of neutral alcohol.

Therefore, the 1-aminoalkylborane (VIII) is apparently the precursor for the neutral alcohol. Based on the hydroboration of olefins, the amount of this intermediate formed would be expected to be a function of the steric influences in a given eneamine. Also, as in the case of olefins, the branching created on formation of the eneamine-borane complex should not affect the orientation of the adding diborane (12). Neither would the orientation be influenced by the electronic effects of the amino group, since these would be masked by the complex. As would be expected from these considerations, 4-(2-ethyl-1-butenyl)morpholine

gave an 82% yield of the neutral alcohol, 4-(1-heptenyl)morpholine a 43% yield of neutral alcohol, and 1-(1-cyclohexenyl)piperidine very little neutral alcohol; these are listed in the order of increasing substitution around the N substituted carbon.



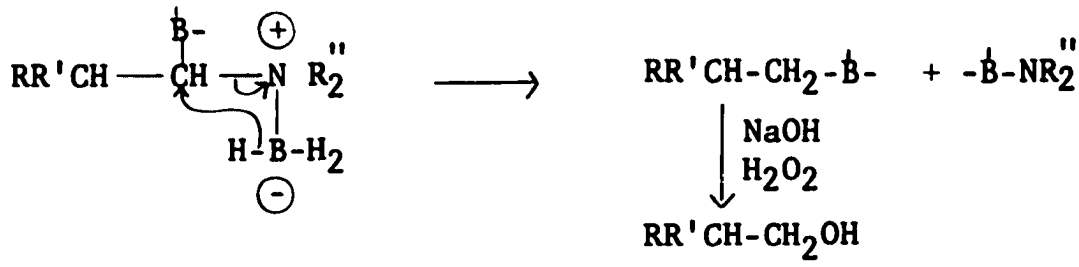
(VII)



(VIII)

An alkylborane, which would proceed to the alcohol on oxidation, could be obtained from the 1-aminoalkylborane as a result of an intramolecular deamination caused by an attack of a hydride from the amine-borane complex at the geminal carbon (equation 4). A deamination of this type would be comparable sterically to the four-centered reactions observed on numerous occasions in boron chemistry, i.e.: 1. the addition of borane to unsaturated linkages (1); 2. base catalyzed reductive cleavage of carbon-boron bonds to produce hydrocarbons (13); 3. disproportionation of substituted boranes (14); and 4. alkyl transfer reactions involving boron, oxygen and sulfur (15).

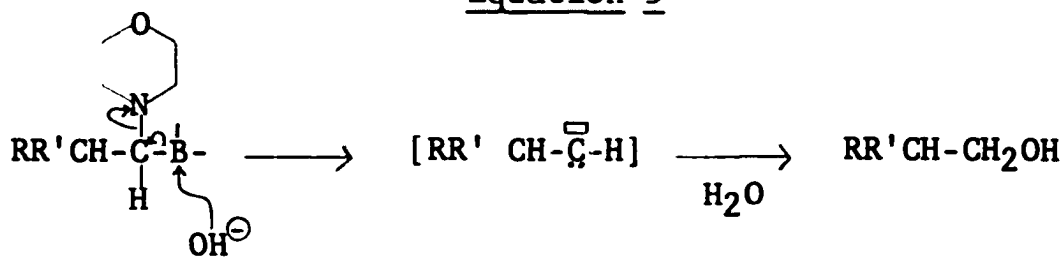
Equation 4



The stoichimetric study seems to rule out a similar deamination involving free diborane (borane not complexed to the amino substituent).

In other possible mechanisms, the aqueous alkaline peroxide treatment might cause the conversion of the 1-amino-alkylborane to the neutral alcohol. For example, elimination could take place as shown below, giving a carbene as the intermediate for the alcohol.

Equation 5



In contrast to all the previous cases, the hydroboration-oxidation treatment of 1-(β-styryl)piperidine simply gave the reduced eneamine, 1-(2-phenylethyl)piperidine (86% yield). The amine was identified by its infrared spectrum, which was identical to that of an authentic sample, and by

the melting point of its hydrochloride salt.

The infrared spectrum showed that the unidentified neutral portion did not contain any 2-phenylethanol.

In the production of 1-(2-phenylethyl)piperidine, boron addition apparently occurred at the benzyl carbon, since benzylboranes dealkylate readily on alkaline hydrolysis to produce the corresponding hydrocarbon (13), while dealkylations at the geminal carbon have not been observed. Also the amount of amine obtained (86%) corresponded quite well to the percentage of α-boron substitution (85%) observed for the hydroboration of the analogous compound, trans-1-phenylpropene (12).

In conclusion, the hydroboration-oxidation of the eneamines derived from ketones gave mainly the corresponding vicinal aminoalcohol with the same stereospecificity observed for olefins. The synthesis, when applied to an eneamine derived from a straight chain aldehyde, gave a smaller yield of the vicinal aminoalcohol, due to the competing deamination. When the eneamine was derived from an aldehyde branched at the α-carbon, the competing reaction dominated and little vicinal aminoalcohol was produced. Thus the hydration appears to be of synthetic value in obtaining sterically pure aminoalcohols, except in the case of an eneamine from alpha disubstituted aldehydes.

EXPERIMENTAL

All melting points and boiling points are uncorrected. The boron trifluoride etherate used was E.K.C. white label. The eneamines derived from aldehydes were prepared by Linda Hensley Kelly.

1-(1-Cyclohexenyl)Piperidine. A solution of 72.5 g. (0.8505 mole) of piperidine and 80 g. (0.815 mole) of cyclohexanone in 200 ml. of benzene was refluxed until the theoretical amount of water (14.8 ml.) was removed by means of a Dean-Stark separator (about 2 days). The benzene was removed and the residue was fractionally distilled to give 93 g. (69% yield) of colorless eneamine, b.p. 78° (0.4 mm), n_D^{25} 1.5105; reported b.p. 108.5° (12 mm.), n_D^{20} 1.5144 (7).

4-(α-Styryl)Morpholine. A solution of 36 g. (0.3 mole) of acetophenone and 26 g. (0.3 mole) of morpholine in 200 ml. of toluene was heated at reflux until the theoretical amount of water (5.4 ml.) was removed (about 8 days). Fractional distillation gave 35 g. (61.5% yield) of colorless

eneamine, n_D^{25} 1.5570, b.p. 95-95° at 0.5 mm. The infrared spectrum had a strong absorption at 8.9 μ attributed to the ether linkage of the morpholine group. This eneamine was observed to decompose and turn yellow on standing for about 1.5 hours, and no elemental analysis was performed.

A solution of 2.23 g. of the freshly distilled eneamine in absolute ethanol was shaken under 24 p.s.i. of hydrogen with 0.1 g. of platinum oxide for one hour. After filtration and removal of solvent, 2.25 g. of colorless 4-(α-methylbenzyl)morpholine was obtained, n_D^{25} 1.5240; reported n_D^{25} 1.5273 (16).

The hydrochloride was prepared by passing dry hydrogen chloride through a solution of 0.9 g. of the amine in 20 ml. of ether. One recrystallization from ethanol-ethyl acetate gave 0.8 g. of 4-(α-styryl)morpholine hydrochloride, m.p. 211-212°; reported m.p. 211-212° (16).

4-(1-Phenyl-1-Propenyl)Morpholine. A solution of 75.5 g. (0.565 mole) of propiophenone and 49 g. (0.565 mole) of morpholine in 200 ml. of benzene was refluxed until the theoretical amount of water was removed (about 9 days). Fractional distillation gave 67 g (59% yield) of colorless eneamine, n_D^{25} 1.5495, b.p. 93-94° (0.4 mm.). The infrared spectrum of the product displayed peaks at 6.12 μ and 8.95 μ,

characteristic respectively of the carbon-carbon double bond and the ether linkage of morpholine. This eneamine turned yellow and decomposed on standing for about one hour, and was not submitted to elemental analysis.

Freshly distilled eneamine (12.4 g.) in 25 ml. of absolute ethanol was hydrogenated under 36 p.s.i. of hydrogen in the presence of 0.4 g. of platinum oxide for 1 hour. After filtration and removal of the solvent, 12.5 g. of colorless liquid, n_D^{25} 1.5220, was obtained. Distillation gave 11.3 g. of colorless 1-(4-morpholino)1-phenylpropane, b.p. 105-108° (12 mm.), n_D^{25} 1.5220.

Dry hydrogen chloride passed through a solution of the amine (1.5 g.) in 40 ml. of ether produced 1.8 g. of white crystals, m.p. 218-220°. One recrystallization from ethanol-ethyl acetate gave 1.2 g. of 1-(4-morpholino)1-phenylpropane hydrochloride, m.p. 221-222°, unchanged by further recrystallizations.

Anal. Calcd. for $C_{13}H_{20}NOCL$:

C, 64.61; H, 8.32; N, 5.80; Cl, 14.65

Found: C, 64.79; H, 8.14; N, 6.06; Cl, 14.65

4-(1-Heptenyl)Morpholine. This eneamine was made according to the procedures of Mannich (5,6,7). Morpholine (87 g., 1 mole) and anhydrous potassium carbonate (1 mole,

138 g.) were placed in a flask equipped with a stirrer, thermometer, and addition funnel and continuously swept with dry nitrogen. The mixture was cooled to -10° by means of a methanol-ice bath, and 57 g. (0.5 mole) of heptanal was added dropwise at such a rate as to maintain the temperature at less than 0°. After the addition was complete, the reaction was allowed to come slowly to room temperature and then stirred an additional 2.5 hours. The diamine was separated from the potassium carbonate by rapid filtration, then placed in a flask equipped with a distillation column and pyrolyzed under a reduced pressure of 20 mm. at an oil bath temperature of 120°. As the pyrolysis proceeded, the morpholine eliminated was collected. After the morpholine ceased to be evolved (1 to 2 hours), the eneamine was distilled to give 70 g. (77% yield) of colorless liquid, n_D^{25} 1.4740, b.p. 125-126° (12 mm.); reported n_D^{25} 1.4768, b.p. 118° at 12 mm. (7).

4-(2-Ethyl-1-Butenyl)Morpholine. In the same manner as above, 50 g. (0.5 mole) of freshly distilled 2-ethylbutyraldehyde was treated with 87 g. (1 mole) of morpholine in the presence of 138.2 g. (1 mole) of anhydrous potassium carbonate. The diamine obtained after filtration was pyrolyzed under reduced pressure of 20 mm. at an oil bath temperature of 90 to 100°. After the morpholine ceased to come

over (1 to 2 hours), the eneamine was distilled at 90-91° (8 mm.) to give 61 g. (74%) of colorless liquid, n_D^{25} 1.4660. The infrared spectrum had absorption peaks at 6.05 and 9.02 μ, characteristic respectively of the carbon-carbon double bond and the other linkage of the morpholine group.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.95; H, 11.32; N, 8.46

Found: C, 70.41; H, 11.23; N, 8.40

1-(β-Styryl)Piperidine. In the same manner as in the previous two experiments, 63 g. (0.525 mole) of freshly distilled phenylacetaldehyde, 90 g. (1.2 mole) of piperidine and 147 g. of anhydrous potassium carbonate gave the corresponding diamine that was pyrolyzed under a pressure of 20 mm. and at an oil bath temperature of 120-129°. Piperidine ceased to be eliminated after 1 to 2 hours. Distillation gave 67 g. (63%) of yellow liquid, 1-(β-styryl)piperidine, b.p. 133-135° at 0.4 mm.; reported b.p. 124-125° at 0.4 mm. (6). The product solidified on standing, m.p. 29-31°; reported 29° (6).

A solution of 4.4 g. of the eneamine in 35 ml. of absolute ethanol was shaken with 0.4 g. of platinum oxide under 35 p.s.i. of hydrogen. After filtration and removal of solvent, 4.5 g. of colorless liquid, 2-(1-piperidino)1-phenylethane (n_D^{25} 1.5209) was obtained.

Dry hydrogen chloride passed through 0.9 g. of the above amine in ether solution produced, after one recrystallization from ethanol-ethyl acetate, 0.9 g. of 1-(2-phenylethyl)piperidine hydrochloride, m.p. 232-233°; reported m.p. 232-233° (17).

Hydroboration of the Eneamines, Followed by Alkaline Hydrogen Peroxide Treatment. The hydroborations of the eneamines were carried out in situ. A flask, equipped with a stirrer, reflux condenser and a rubber septum, was swept continuously by dry nitrogen that exited into an acetone bath (used to trap any diborane carried over). Dry tetrahydrofuran (250 ml.) and 8 g. (0.212 mole) of sodium borohydride were added to the flask after sweeping with nitrogen for 1.5 hours. Boron trifluoride etherate (56 ml., about 0.44 mole) was then added over 15 to 25 minutes through the septum by means of a syringe. With this slow addition, no rise in temperature was observed. The reaction mixture was stirred for 1 hour, then cooled by an ice bath and 6-10.5g. of freshly distilled eneamine was introduced by syringe. The bath was removed and the hydroboration was allowed to proceed with stirring at room temperature for 1-3 hours. The reaction flask was then cooled by an ice bath and 25% sodium hydroxide solution (110-130 ml., 0.69 to 0.82 mole of sodium

hydroxide) was added over 10 to 15 minutes until the reaction had a pH of 10. The bath was removed and the whole allowed to come to room temperature at which time 30% hydrogen peroxide (12-15 ml., 0.12 to 0.14 mole of hydrogen peroxide) was added. The reaction mixture was then refluxed with stirring on a steam bath for 2 to 6 hours. Although not detected earlier, two liquid phases were observed during refluxing.

After about 0.5 hours of refluxing, the nitrogen source and acetone bath were removed. At the end of the alkaline hydrogen peroxide treatment, the reflux condenser was replaced by a Vigreux column and the tetrahydrofuran was removed by distillation. The flask was then cooled to room temperature and 75 ml. of ether was added with stirring. The reaction mixture was filtered to remove the inorganic salts, and the filtrate separated into organic and aqueous phases. The inorganic salts and the aqueous layer were washed four times with the same 35 ml. portions of ether, which were combined with the main ether layer. To extract the amine, the combined organic phase was washed with three 50 ml. portions of ice cold 0.64 N hydrochloric acid. The ether solution was then washed with water until the washings were neutral to pH paper, dried over sodium sulfate and the ether

removed to give the neutral fraction of the reaction. The combined acid washings were made basic to a pH of 10 with 25% sodium hydroxide solution, and the precipitated amine extracted with five 30 ml. portions of ether. The combined ether extracts were washed with water, dried over sodium sulfate, and the ether removed to give the basic fraction of the reaction.

Reaction of 1-(1-Cyclohexenyl)Piperidine. From the reaction of 8.5 g. of 1-(1-cyclohexenyl)piperidine, 8.3 g. (88%) of white crystalline trans-2-(1-piperidino)cyclohexanol (m.p. 35-36°) was obtained; reported m.p. 34° (18). No suitable solvent was found for recrystallization. However, as shown by elemental analysis and melting point, this material was pure.

Anal. Calcd. for $C_{11}H_{21}NO$:

C, 72.08; H, 11.55; N, 7.64

Found: C, 71.86; H, 11.61; N, 7.48

The hydrochloride, m.p. 282-283°, was prepared by passing dry hydrogen chloride through an ether solution of the trans aminoalcohol; reported m.p. 280-282° (19).

The light brown, neutral fraction (0.38 g.) was distilled at 160-175° (1 atm.) to give 0.22 g. of colorless liquid whose infrared spectrum was identical to that of

cyclohexanol except for a slight carbonyl peak. However, the 3,5-dinitrobenzoate of the distilled material, prepared from the acid chloride according to the procedure of Shriner, Fuson and Curtin (20), melted over a range of 75-88°, after four recrystallizations from ethanol; reported m.p. of cyclohexyl-3,5-dinitrobenzoate, 109-111° (20).

Reaction of 4-(α-Styryl)Morpholine. The hydroboration oxidation of 10.6 g. of 4-(α-styryl)morpholine gave 9.4 g. (81%) of the crude vicinal amonoalcohol, n_D^{25} 1.4525. Distillation at 125-130° (0.5 mm.) yielded 8.25 g. (71%) of colorless 2-(4-morpholine)2-phenylethanol, n_D^{25} 1.4555. The infrared spectrum of the product displayed an alcohol absorption at 2.95μ and the strong ether absorption peak of morpholine at 8.95μ. Previous experiments, employing eneamine which stood 3 to 6 hours after distillation, gave 45 to 60% yields of the vicinal aminoalcohol.

Anal. Calcd. for $C_{12}H_{17}NO_2$:

C, 69.54; H, 8.27; N, 6.76

Found: C, 69.48; H, 8.23; N, 6.65

The above aminoalcohol (0.5 g.) in 10 ml. of ethanol was added to 10 ml. of a concentrated ethanol solution of picric acid, and the resulting solution heated to boiling on a steam bath. Upon cooling to 0°, 1.3 g. of yellow crystals

were obtained, m.p. 197-202° (dec.). After three recrystallizations from ethanol, 0.75 g. of picrate derivative was obtained, m.p. 199-202° (dec.).

Anal. Calcd. for $C_{18}H_{20}N_4O_9$:

C, 49.54; H, 4.62; N, 12.84; O, 33.00

Found: C, 49.89; H, 4.77; N, 12.59; O, 32.89

The neutral portion of this reaction yielded 0.4 g. of yellow, viscous oil whose infrared spectrum had both carbonyl and hydroxyl absorptions.

Reaction of 4-(1-Phenyl-1-Propenyl)Morpholine. From the basic fraction of the hydroboration-oxidation of 6.84 g. of eneamine, 6.6 g. (88.6%) of white crystalline 1-(4-morpholino)1-phenyl-2-propanol, m.p. 94-96°, was obtained. Its infrared spectrum had a hydroxyl absorption at 2.92 μ and a strong ether absorption from the morpholine group at 8.95 μ. The elemental analysis given below indicated this material to be pure. Recrystallization of 1.1 g. from ether gave 0.9 g. of material, m.p. 94.5-97°.

Anal. Calcd. for $C_{13}H_{19}NO_2$:

C, 70.55; H, 8.65; N, 6.33

Found: C, 70.44; H, 8.60; N, 6.43

Dry hydrogen chloride gas was bubbled through a solution of 1 g. of the above aminoalcohol in 20 ml. of ether and

after filtration, 1.1 g. of the hydrochloride, m.p. 216-217°, was collected. One recrystallization from ethanol-acetone solution raised the melting point to 216.5-218°.

Anal. Calcd. for $C_{13}H_{20}NO_2Cl$:

C, 60.69; H, 7.82; N, 5.44; Cl, 13.75

Found: C, 60.95; H, 7.91; N, 5.38; Cl, 13.58

The neutral fraction amounted to 0.33 g. of very viscous, brown oil. The infrared spectrum of this oil showed both hydroxyl and carbonyl absorptions.

Reaction of 4-(1-Heptenyl)Morpholine. From the reaction of 7.3 g. of the eneamine, the basic fraction gave 3.9 g. of a colorless liquid (n_D^{25} 1.4590) whose infrared spectrum had characteristic alcohol and ether absorptions at 2.82 and 8.95 μ respectively. The aminoalcohol, 1-(4-morpholino)2-heptanol, was distilled at 105-110° (1 mm.) to give 3.6 g. (45%) of colorless product, n_D^{25} 1.4580.

Anal. Calcd. for $C_{11}H_{23}NO_2$:

C, 65.63; H, 11.52; N, 6.96

Found: C, 65.41; H, 11.34; N, 7.13

An ethanol solution of 1 g. of the above aminoalcohol was added to 15 ml. of a concentrated ethanol solution of picric acid and the solution obtained heated to boiling on a steam bath. After cooling to 0°, 2 g. of yellow crystalline

picric acid derivative, m.p. 105-108°, was collected by filtration. One recrystallization from ethanol gave 1.8 g. of material melting at 107-108°, which was unchanged by further recrystallizations.

Anal. Calcd. for $C_{17}H_{26}N_4O_9$:

C, 47.44; H, 6.09; N, 13.02

Found: C, 47.50; H, 5.92; N, 13.23

The neutral fraction yielded 2.30 g. of yellow oil. Distillation of this crude oil gave 2.00 g. (43%) of 1-heptanol, b.p. 168-173° (1 atm.), n_D^{25} 1.4425; reported b.p. 177° (1 atm.), n_D^{20} 1.4445 (21). The brown, viscous, oily residue amounted to 0.25 g. The α-napthylurethane was made from the alcohol according to the procedure of Shriner, Fuson and Curtin (20), m.p. 60-61°; reported m.p. 61° (20). The infrared spectrum of the alcohol was identical to that of a commercial sample of 1-heptanol. Comparison of vapor phase chromatographic retention times of 1 and 2-heptanol on a column (6' x ¼") packed with 20% LAC 296 on Anakrom with that of the neutral, distilled fraction, indicated the absence of 2-heptanol.

Ex-Situ Hydroboration of 4-(1-Heptenyl)Morpholine. Boron trifluoride etherate (35 ml.) was added with stirring over 2.5 hours to a suspension of lithium aluminum hydride

(5.5 g.) in 50 ml. of ether. The diborane (0.195 mole) generated in this fashion was swept by nitrogen into a second flask where it passed through a solution of 4-(1-heptenyl)-morpholine (7.2 g., 0.0392 mole) in 150 ml. of tetrahydrofurane. After the addition of the boron trifluoride etherate, sweeping was continued for another 2.5 hours. The alkaline peroxide treatment was carried out by refluxing for 2 hours on a steam bath. Seventy ml. of 10% sodium hydroxide (0.175 mole) and 15 ml. of 30% hydrogen peroxide (0.14 mole of hydrogen peroxide) were used.

In contrast to the in situ reaction, only one liquid phase was present and no precipitation occurred. After the tetrahydrofuran was removed, the reaction was divided into basic and neutral fractions. By means of infrared spectroscopy, the basic fraction was shown to be crude vicinal amino-alcohol (3.93 g., 50%) and the neutral portion to be crude 1-heptanol (2.1 g., 46%).

Reaction of 4-(2-Ethyl-1-Butenyl)Morpholine. The basic fraction of the reaction of 7.12 g. of 4-(2-ethyl-1-butenyl)morpholine yielded 1.00 g. (12.7%) of a colorless material whose infrared spectrum showed a hydroxyl absorption at 2.90μ and a strong ether absorption from the morpholine group at 8.97μ. The colorless liquid was distilled at

90-97° (5 mm.) to give 0.85 g. of colorless product, n_D^{25} 1.4600. This liquid was apparently a mixture of amines, since the picrate derivative, obtained from 0.3 g. of distilled material, gave after three recrystallizations from ethanol, 0.25 g. of yellow crystals melting at 145-155°.

Distillation of the crude neutral fraction at 150-155° (1 atm.) yielded 3.5 g. (82%) of 2-ethylbutanol, n_D^{25} 1.4190 (commercial sample, n_D^{25} 1.4190). The infrared spectrum of this alcohol was identical to that of the commercial sample, and the 3,5-dinitrobenzoate made according to the procedure of Shriner, Fuson and Curtin (20), melted at 50-51°; reported m. p. 51° (20).

Stoichiometric Study, Eneamine-Borane Ratio of 1:1.17. An in situ hydroboration of 4-(2-ethyl-1-butenyl)-morpholine was carried out for 1 hour in a ratio of eneamine to borane (BH_3) of 1 to 1.17. This was achieved by using 150 ml. of tetrahydrofuran as solvent, 0.37 g. (0.0098 mole) of sodium borohydride, 1.8 ml. of boron trifluoride etherate (0.014 mole) and 1.9 g. (0.0112 mole) of eneamine. The oxidative treatment was performed by refluxing the product of the above on a steam bath for 2 hours with 40 ml. of 12% sodium hydroxide (0.12 mole) and 4 ml. of 30% hydrogen peroxide (0.129 mole). The infrared spectrum of the basic fraction

(1.1 g.) was identical to that of the eneamine and no bands unique to the basic fraction of the preparative reaction were present. The neutral fraction (0.33 g.) had an infrared spectrum identical to that of 2-ethylbutanol except for a carbonyl band at 5.8μ, which is the same position for the carbonyl absorption of 2-ethylbutyraldehyde. These data indicate that only partial hydroboration took place.

Stoichiometric Study, Eneamine-Borane Ratio of 1:1.38. In a second experiment, the molar ratio of eneamine to borane was 1 to 1.38. The hydroboration was carried out for 2 hours in 150 ml. of tetrahydrofuran, using 0.5 g. (0.01325 mole) of sodium borohydride, 0.0177 mole of boron trifluoride etherate and 2.15 g. (0.0127 mole) of eneamine. The alkaline peroxide oxidation was performed by refluxing on a steam bath for 2 hours, using 50 ml. of 10% sodium hydroxide (0.125 mole) and 4 ml. of 30% hydrogen peroxide (0.129 mole). The infrared spectrum of the basic fraction (0.30 g., 12.6%) did not show any absorption bands unique to the eneamine. The neutral fraction was composed of 1.1 g. (85%) of crude 2-ethylbutanol as shown by the infrared spectrum. These data indicated that complete reaction occurred.

Reaction of 1-(β -Styryl)Piperidine. From 7.9 g. of

eneamine, 6.85 g. (85.5%) of 1-(2-phenylethyl)piperdine was obtained, n_D^{25} 1.5211. The infrared spectrum of the colorless liquid was identical to that of an authentic sample produced from the hydrogenation of the eneamine. The product was distilled to give 6.6 g. of colorless 1-(2-phenylethyl)piperidine, n_D^{25} 1.5217, b.p. 115-120° (2 mm.); reported b.p. 127-128° at 10 mm. (17).

Dry hydrogen chloride passed through a solution of the amine in ether gave the hydrochloride, which melted at 232-233° after one recrystallization from ethanol-ethyl acetate. The melting point was undepressed when mixed with an authentic sample.

The neutral fraction, although not identified, did not show hydroxyl or carbonyl absorptions in the infrared spectrum.

SUMMARY

The hydroboration-oxidation of eneamines derived from ketones and aldehydes was investigated. The eneamines obtained from ketones and secondary amines were 1-(1-cyclohexyl)piperidine, 4-(α-styryl)morpholine, and 4-(1-phenyl-1-propenyl)morpholine. The hydroboration-oxidation of these eneamines, as in the case of olefins, gave mainly anti-Markownikoff cis hydration of the carbon-carbon double bond.

The eneamines derived from aldehydes and secondary amines were 4-(1-heptenyl)morpholine, 4-(2-ethyl-1-butenyl)-morpholine, and 1-(β-styryl)piperidine. The reaction of 4-(1-heptenyl)morpholine gave the corresponding vicinal amino-alcohol in 45% yield and an unexpected product, heptanol, in 43% yield. The reaction of 4-(2-ethyl-1-butenyl)morpholine produced 2-ethylbutanol in 82% yield and a small amount of basic material.

Hydroboration using a molar ratio of 1 to 1.17 of 4-(2-ethyl-1-butenyl)morpholine to borane gave essentially no

reaction, indicating formation of the eneamine-borane complex. Complete reaction occurred with a molar ratio of 1 to 1.38.

Consideration was given to the formation of the neutral alcohols from the corresponding olefins, which might be obtained from the appropriate 2-aminoalkylborane by an elimination reaction. However, experimental results did not favor this route. A more likely precursor for the neutral alcohol is the 1-aminoalkyborane. Two paths were proposed for the formation of alcohol from this intermediate.

Hydroboration and oxidation of 1-(β-styryl)piperidine gave 1-(2-phenylethyl)piperidine in 85% yield, apparently by reductive dealkylation of the benzylborane.

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